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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,505	NEXO ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,15-30,32-35 and 37* is/are pending in the application.

4a) Of the above claim(s) *25-30,32-35 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 15-30, 32-35, and 37 are pending.
Claims 11-14, 31, and 36 are cancelled.
Claims 25-30, 32-35, and 37 are withdrawn.
Claims 1-10 and 15-24 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group 1 (methods for estimating cancer risk based on nucleic acid analysis) in the reply filed on 06/11/2007 is acknowledged. Applicants further election of SEQ ID NO: 92 (relevant to the Further Lack of Unity Restriction Requirement) is also acknowledged. The traversal is on the ground(s) that the groups made by the examiner are linked by a single inventive concept. As addressed in the Requirement for Restriction, the common technical feature of a sequence polymorphism in SEQ ID NO: 2 is not a novel feature in view of the prior art. Applicants further argue that, with regard to Group 1 (nucleic acid based methods) and Group 2 (protein based methods), a protein and DNA encoding the protein have 'corresponding special technical feature' and thus have unity in PCT practice. This is not found persuasive because in the instant case the claims of Group 1 and Group 2 are not drawn to polypeptides and the nucleic acids that encode the polypeptides, but rather to methods requiring assessing sequence polymorphisms in a region corresponding to SEQ ID NO: 2 or in a translation product from a sequence in a region corresponding to SEQ ID NO: 2, where the methods for nucleotide versus translation product analysis require structurally distinct reagents (e.g.: oligonucleotide probes versus epitope-specific antibodies) as well as diverse methodological steps (e.g. nucleic acid hybridization versus western blot analysis).

It is noted that SEQ ID NO: 92 and SEQ ID NO: 195 are identical, and as such the Lack of Unity among these two particular subsequences is withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-30, 32-35, and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/11/2007.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code: see for example p.13 ln.26 and p.17 ln.19. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Drawings

3. The drawings are objected to because

Fig 3 of the drawings provides two points of the curve both labeled as '12', located at different chromosome positions. Page 48 of the specification provides information pertaining to curves indicating that '12' is SLC1A5e8, which does not have two different chromosomal locations. Appropriate correction of the figure is required.

Fig 4 provides the sequence of a portion of the S1, S2, and S3 regions of SEQ ID NO: 2, but the description of the drawing on page 8 of the specification does not indicate, by nucleotide position numbers, what portion of SEQ ID NO: 2 is represented in Fig 4. Appropriate correction may be made by including the nucleotide position numbers in the description of the drawing.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claims 1 and 2 are objected to for the specific recitation of non-elected subject matter. Applicants have elected for the examination of claims drawn to the analysis of nucleic acid sequences. Claims 1 and 2 recite analysis of a 'translation product from a sequence'. Prior to allowance of these claims, the non-elected subject matter will be required to be deleted from the claims.

5. Claims 18-20 are objected to for the specific recitation of non-elected subject matter. Applicants have elected for the examination of claims drawn to the analysis of the subsequence of SEQ ID NO: 92. Claims 18-20 recite various specific non-elected SEQ ID NOs in reference to non-elected subsequences. Prior to allowance of these claims, the non-elected subject matter will be required to be deleted from the claims.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-10 and 15-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 and 15-24 are unclear over recitation of the phrase 'obtaining a sequence polymorphism response', as recited in claim 1. It is unclear what active steps are required to obtaining a sequence polymorphism response. It is unclear if a 'response' is dictated by specific structural or functional limitations of any sequence polymorphism. Additionally, the relationship between, assessing a sequence polymorphism, obtaining a response, and estimating a cancer risk (as recited in the preamble of claim 1) is unclear.

Claim 2 is unclear because the claim is dependent upon claim 1, but claim requires only that a polymorphism in SEQ ID NO: 1 is assessed. It is not clear if the

claim requires analysis of any sequence polymorphism in SEQ ID NO: 2, as recited in claim 1.

Claim 3 is unclear over recitation of the phrase 'the cell sample', because there is not proper antecedent basis in either claim 3, or claim 1 from which claim 3 depends, for any 'cell sample'. The claim may be made more clear if the unclear phrase is amended to recite 'the ~~cell~~ sample'. See MPEP 2173.05(e).

Claim 4 is unclear over recitation of the phrase 'the cell', because there is not proper antecedent basis in either claim 4, or claim 1 from which claim 3 depends, for any 'cell'. Further more it is noted that 'tumor tissue' is not a 'cell'. See MPEP 2173.05(e).

Claim 16 is unclear over recitation of the phrase 'the nucleotide primer or probe', because there is no antecedent basis for any 'nucleotide primer or probe' in either claim 16, or claim 15 from which claim 16 depends. Claim 15 recites only 'nucleic acid primer or probe'. See MPEP 2173.05(e).

Claims 18-20 are unclear over recitation of the phrase 'at least one primer or probe' as recited in claim 18, because claim 18 is dependent upon claim 15 which specifically recites 'nucleic acid primer or probe'. As such claims 18-20 are broader in scope than claim 15, from which the claims depend.

Claim 19 is unclear over recitation of the phrase 'nucleotide probe', because there is no antecedent basis for any 'nucleotide probe' in either claim 18 or claim 15 from which claim 19 depends. Claim 15 recites only 'nucleic acid primer or probe', and claim 18 recites only 'primer or probe'. See MPEP 2173.05(e).

Claim Rejections - 35 USC § 112 1st ¶ - Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-10, 15-17, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods for any estimation of skin, lung, breast, or colon cancer risk comprising the detection of any sequence polymorphism in SEQ ID NO: 2, where SEQ ID NO: 2 of the instant application encompasses 37,790 bases of human chromosome 19. As such the claims encompass methods comprising the assessment of a practically infinitely large genus of nucleic acid sequences wherein the assessed sequence polymorphisms are not defined by any structural limitations. Polynucleotides of such a large genus, with the required functionality of being suitable for estimating cancer risk of an individual, have not been described in the instant specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described

by their complete structure. Relevant to the instant claims and their rejection for lack of adequate written description, the instant specification provides only the particular sequences derived from human chromosome 19 of the 37,790 bases of SEQ ID NO: 1, the 38,166 bases of SEQ ID NO: 2 (where SEQ ID NO: 2 encompasses SEQ ID NO: 1), and variants thereof as specifically exemplified by the 21 polymorphisms (as specified by sequence context and particular polymorphic nucleotide content) listed in Table 1c as being present in SEQ ID NO: 1 or 2 referenced as SEQ ID NOs: 183, 184, 186-195, and 197-205. However, in considering the breadth of the claimed invention, the claimed methods encompass the assessment of any variant nucleotide content in, for example the 38,166 bases of SEQ ID NO: 2. Even if one were only to consider, for example, bi-allelic sequence polymorphisms taken individually over the length of SEQ ID NO: 2 (i.e. any position in SEQ ID NO: 2 can be one of two different nucleotides), the claims encompass analysis of 76,332 different sequences. However, the claims are much broader as the claims encompass any combinations of any number of single or multiple nucleotide substitutions, insertions, deletions, or gene rearrangements. And while the breadth of the claims is not limited by any particular sequence polymorphisms, the specification teaches only a very limited number of particular polymorphisms. The divide between the teachings of the specification and the breadth of the claims is exemplified in a comparison between the teachings of the specification, which demonstrates 9 polymorphisms in the RAI gene (Table 1c, SEQ ID NOs: 191-199), whereas the GeneCard output for the RAI gene (referred to as PPP1R13L by GeneCard) indicates at least 141 polymorphisms associated with this gene.

In analyzing whether the written description requirement is met for genus claims, it is next determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. The instant application does not provide any characteristics of a sequence polymorphism that would allow the skilled artisan to determine that any polymorphic nucleotide content, beyond polynucleotides comprising those sequences disclosed in the instant specification, is a sequence polymoprhism suitable for estimating a cancer risk.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the case of the instant claims, the ability to identify any sequence polymorphism as associated with a particular risk of skin, lung, breast, and colon cancer is critical to the claimed invention. And while Applicant has several specific examples of particular sequence polymorphisms, the specification does not provide, by specific structures or characteristic examples, sequence polymorphisms representative of the breadth of the claimed invention. As such one of skill in the art can not a priori identify sequence polymorphisms of SEQ ID NO: 2 with the required functionality of being suitable for estimating a cancer risk.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, the specification does not provide an adequate written description of the claimed subject matter. Note that this rejection is not applied to claims 18-20 which specify the nucleotide content and context of a required sequence polymorphism, consonant with the Election, as SEQ ID NO: 92.

Claim Rejections - 35 USC § 112 1srt ¶ - Scope of Enablement

10. Claims 1-11 and 15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for estimating basal cell carcinoma risk of a human individual comprising:
> obtaining a sample from said individual, said sample comprising genetic material;
> detecting in said genetic material a polymorphic nucleotide content in SEQ ID NO: 2 or the complement of SEQ ID NO: 2; and
> estimating the basal cell carcinoma risk of said human individual based on the detected polymorphic nucleotide content, wherein the detected polymorphic nucleotide content is the homozygous presence of an A at position 21 in both copies of SEQ ID NO: 92, wherein the presence of said detected polymorphic nucleotide content indicates an increased risk of basal cell carcinoma in said individual.

does not reasonably provide enablement for any methods comprising estimating risk in any non-human individuals, estimating risk of disease using any sequence polymorphism anywhere within SEQ ID NO: 2, estimating the risk of any type of skin cancer, or estimating risk of lung, breast, or colon cancer specifically comprising only the analysis of SEQ ID NO: 195 (as consonant with the election). The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

In the analysis of claims for the enablement requirement of 35 USC 112 1st ¶, the claims are analyzed as they are generically drawn to the assessment of any sequence polymorphism within SEQ ID NO: 2, as well in so far as they are drawn to methods specifically requiring only the analysis of the elected polymorphic subsequence of SEQ ID NO: 92. While applicant may assert other enabled embodiments, such as haplotype combinations of specific particular polymorphic content, no such specific combinations are required by any of the claims, and such specific combinations are not a part of the Elected invention of the specific analysis of the subsequence of SEQ ID NO: 92.

Nature of the Invention and Breadth of the Claims

The instant invention is drawn to methods for estimating the risk of skin, lung, breast, and colon cancer.

The claims encompass estimating cancer risk based on any assessment of any sequence polymorphism in SEQ ID NO: 2.

Claims 18-20, consonant with the election, require the specific analysis of only SEQ ID NO: 92, and any estimation base on the detection of any nucleotide content at the variable position of SEQ ID NO: 92 (where position 20 of SEQ ID NO: 92 may be either A or G).

The claims thus require knowledge of a reliable association between any of an extremely large number of possible variations in nucleotide content and the estimated risk of skin, lung, breast, and colon cancer.

Direction provided by the specification and working examples

The instant specification provides an analysis of a specific portion of human chromosome 19q13.2-3 (p.8 lns.28; Fig 1) and the identification and analysis of several specific polymorphic nucleotide positions in SEQ ID NO: 2. The specification does not provide any analysis of sequence polymorphisms in SEQ ID NO: 2 other than the 21 particular polymorphisms of Table 1c. The specification provides no analysis of any proposed functionality of any polymorphisms (e.g. effects on transcription, splicing, or resulting protein activity), and provides only an analysis of the association of particular nucleotide content of specific polymorphic sequences the specific phenotypes of BCC, breast cancer, and lung cancer.

The instant specification provides only the analysis of human samples and subjects, and provides no analysis of any other non-human sequences or subjects.

The instant specification provides only the analysis of basal cell carcinoma (BCC), breast cancer, and lung cancer. The instant specification provides no analysis of any other cancers, including no analysis of colon cancer as specifically recited in the claims.

Regarding the claims, consonant with the Election, in so far as they only specifically require the analysis of the content of subsequence SEQ ID NO: 92 (where SEQ ID NO: 92 has a variable A or G content at position 21 and is referred to in the specification as the RAli1 polymorphism), instant specification provides (Example 2, p.49) only an analysis of this specific subsequence as it relates to BCC. The

specification teaches that the A/A genotype of the RAli1 polymorphism is a high risk genotype, and is indicative of an increased risk of BCC.

The instant specification does not provide any examples of the RAli1 polymorphism with any skin cancers other than BCC.

While the specification provides other analyses that include the RAli1 polymorphism as associated with other phenotypes (i.e. breast and lung cancer), the other analyses require the assessment of the RAli1 polymorphism as part of a specific haplotype (i.e. the RAli1 polymorphism is required to be in combination with other specific polymorphic subsequences that are not a pert of the elected invention). As such, the instant specification does not provide any teaching of the reliable association of the RAli1 polymorphism alone with breast cancer (specification examples 6, 7, 8, and 10) or lung cancer (specification examples 9, 11, 12, and 13).

State of the art, level of skill in the art, and level of unpredictability

While the sate of the art and level of skill in the art with regard to detecting any particular polymorphism in a defined sequence is high, the unpredictability in associating any generic polymorphism in a sequence with a particular phenotype, such as an estimated risk of a particular cancer, is even higher. The unpredictablility is demonstrated by the prior art and the post-filing art.

Because the breadth of the claims encompass the analysis of sequence polymorphisms in any subject organism, while the specification provides only the analysis of humans, it is relevant to point out the unpredictability in extrapolating sequence related data from one organism to any other organism as sequences that

appear quite similar may in fact have very different functionalities. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Because the claims are drawn to the analysis of any generic polymorphism in SEQ ID NO: 2, it is relevant to point out the unpredictability is associating any generic sequence variation with a particular phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Furthermore, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain. This is particularly relevant as the instant specification does not teach any functional consequence of the elected RAli1 variation such that one might extrapolate the BCC association to any other particular or generic sequence variation.

Because the claims are drawn to method comprising the specific analysis only of the subsequence of SEQ ID NO: 92 (i.e. the RAli1 polymorphism) in breast and lung

cancer, whereas the specification provides only the teaching of that particular polymorphic subsequence in a multi-polymorphism haplotype, it is relevant to point out the unpredictability with regard to extrapolating phenotypic associations with individual SNPs from any haplotype. Such unpredictability is exemplified by Davidson (2000), which teaches that in an analysis of nucleotide polymorphisms associated with salbutamol response, individual SNPs were not significantly associated with response, whereas the multi-SNP haplotype was (left col., 2nd ¶).

And while the claims encompass any skin cancer, whereas the specification teaches only BCC, it is relevant to address the unpredictability known in extrapolating the association of any particular SNP with a specific form of skin cancer to any other different form of skin cancer. For example, Han et al (2004) teach that a variation in the XRCC1 gene may be differently associated with skin cancer risk according to skin cancer type (Table 1). As such it is unpredictable as to how one might estimate the SCC cancer risk based on the BCC data of the instant specification.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the invention in the full scope of the claims. One would be require to perform case:control studies in different types of organisms to determine the manner in which any possible variation of SEQ ID NO: 2 could be used to estimate the risk of any skin cancer, or breast, lung, or colon cancer. Furthermore, even with the elected invention, oun would be required to perform case:control experimentation to determine that the RAli1 variation of the instant specification is associated with any type of skin cancer

other than BCC, and that RAli1 by itself (i.e. not as part of a larger haplotype) is associated with lung or breast cancer, or that there is any association with colon cancer. Even if one were to perform such experimentation, there is no assurance that any additional particular associations, beyond those particular associations recognized in the instant specification, would be identified.

Conclusion

After consideration of the teaching of the specification and the specific working examples, considering the breadth of the claims, and the unpredictability in the art, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Conclusion

11. No claim is allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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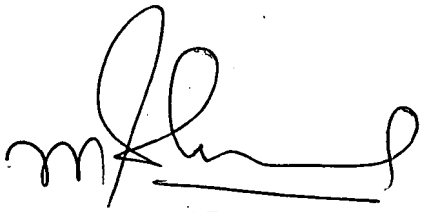
Stephen Kapushoc
Art Unit 1634



RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER